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PATENT TRADEMARK OFFICE

Docket No: 3153/1E974-US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Divisional Application of: Charles F. SPENCE; Anne Y. FU; Stephen R. QUAKE; Frances H. ARNOLD

Serial No.: To be assigned[1] Art Unit: 1743

Filed: Herewith Examiner: John S. STARSIAK

For: MICROFABRICATED CELL SORTER FOR CHEMICAL AND BIOLOGICAL MATERIALS

PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.111

Hon. Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

In accordance with Rule 111 of the Rules of Practice, please enter the following amendments and consider the accompanying remarks in connection with the above-captioned patent application. These amendments are made pursuant to the requirements of 37 C.F.R. § 1.121. Accordingly, Applicants are submitting herewith, as Exhibit A, a copy of the amended claims marked up, as required under

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[1] The above-captioned patent application is a divisional of U.S. Patent Application Serial No. 09/325,667 filed May 21, 1999.

37 C.F.R. § 1.121(c)(ii), to show all changes relative to the previous version of each claim.

Please amend the application as follows:

IN THE SPECIFICATION:

Delete the paragraph on page 1 at lines 4-8 of the specification filed herewith, and enter the following new paragraph with the changes indicated in the accompanying Exhibit A:

-- This application is a divisional of copending U.S. Patent Application Serial No. 09/325,667 filed on May 21, 1999 (hereinafter "the '667 application"). The '667 application, in turn, claims the benefit of priority from U.S. Patent Application No. 08/932,774, filed September 23, 1997 (now U.S. Patent No. 6,221,654 B1, issued April 24, 2001) and is a continuation-in-part thereof. The '667 application also claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/108,894 filed November 17, 1998; and to U.S. Provisional Application No. 60/086,394 filed May 22, 1998. Each of these priority applications is incorporated herein by reference in its entirety. --

IN THE CLAIMS:

Cancel claims 1 and 38 without prejudice.

Amend claims 2-14, 16, 18-28, 31-35, 39-43, 49 and 50, as indicated in the attached Exhibit A, and add new claims 51-54 so that the pending claims are as follows:

2. (Amended) A device of claim 51, wherein at least one of the main and branch channels communicates with a reservoir.

3. (Amended) A device of claim 51, wherein the substrate is comprised of silicon.

4. (Amended) A device of claim 51, wherein the substrate comprises a silicone elastomer.

5. (Amended) A device of claim 51 wherein the particles of biological material comprise cells.

6. (Amended) A device of claim 4 wherein the silicone elastomer substrate is made from an impression of an etched silicon wafer.

7. (Amended) A device of claim 51 wherein the flow control system is electro-osmotic.

8. (Amended) A device of claim 51 wherein the flow control system is electrophoretic.

9. (Amended) A device of claim 51 wherein the flow control system is dielectrophoretic.

10. (Amended) A device of claim 51 wherein the flow control system is pressure driven.

11. (Amended) A device of claim 51 wherein the flow control system is microvalve.

12. (Amended) A device of claim 51 wherein the flow control system is optical trapping.

13. (Amended) A device of claim 51 wherein the flow control system is flow stoppage-based control.

14. (Amended) A device according to claim 51 wherein the flow control is provided by a voltage gradient between the branch channels and the junction.

15. A device according to claim 14 wherein the voltage gradient is generated by electrodes in the branch channels.

16. (Amended) A device of claim 51 wherein the flow control is by a pressure gradient between one or more channels and the junction.

17. A device of claim 16 wherein pressure driven flow control is provided by capillary action at one or more channels of the substrate.

18. (Amended) A device of claim 51 wherein the flow control comprises one or more valves.

19. (Amended) A device of claim 51 wherein the flow control comprises one or more valves.

20. (Amended) A device of claim 51 wherein the flow control is reversible.

21. (Amended) A device of claim 52 wherein the characteristic is optically detectable.

22. (Amended) A device of claim 52 wherein the characteristic is determined by a fluorescent reporter.

23. (Amended) A device of claim 52 wherein the characteristic is determined by a chemiluminescent reporter.

24. (Amended) A device of claim 52 wherein the characteristic is determined by a radioactive reporter.

25. (Amended) A device of claim 52 wherein the characteristic is determined by a spectroscopically detectable reporter.

26. (Amended) A device according to claim 52 wherein the predetermined characteristic is size.

27. (Amended) A device of claim 52 wherein the detection apparatus comprises a light scattering apparatus.

28. (Amended) A device of claim 52 wherein the detection apparatus comprises an apparatus for recognizing electromagnetic radiation.

29. A device of claim 28 wherein the detection apparatus further comprises a source of electromagnetic excitation.

30. A device of claim 29 wherein the excitation source is a light source and the recognizing apparatus is a charge coupled device.

31. (Amended) A device of claim 52 wherein the detection apparatus comprises at least one of photomultiplier tubes and photodiodes.

32. (Amended) A device of claim 52 wherein the detection apparatus is positioned to target biological materials within a predetermined detection region.

33. (Amended) A device of claim 51, wherein the width and height of a channel of the device is at least about two times as large as the diameter of the largest material to be sorted.

34. (Amended) A device of claim 51, wherein a channel is from about 20 μm to 200 μm wide and about 20 μm to 200 μm deep.

35. (Amended) A device of claim 51, wherein the biological material is a cell having a predetermined characteristic that is identified according to a reporter

signal selected from a dye, fluorescent agent, chemiluminescent agent, chromophore, radio-isotope, and optically detectable protein.

36. A device of claim 35, wherein the control of flow is selected from electro-osmotic, electrophoretic, dielectrophoretic, pressure driven, microvalve, laser trapping and flow stoppage-based control.

37. A device of claims 36 wherein the control of flow is reversible.

39. (Amended) A method of claim 54 wherein the width and height of each channel is at least about two times as large as the diameter of the largest cell in the sample of cells.

40. (Amended) A method of claim 54 wherein the predetermined characteristic is an optically detectable reporter in or on the cells.

41. (Amended) A method of claim 54 wherein the cells are interrogated by at least one device selected from the group of microscopes, diodes, light stimulating devices, lasers, light scattering apparatuses, electromagnetic excitation sources, electromagnetic radiation detector apparatuses, photomultiplier tubes, and processors.

42. (Amended) A method of claim 54 wherein the reporter is selected from a dye, fluorescent agent, chemiluminescent agent, chromophore, radio-isotope, and optically detectable protein.

43. (Amended) A method of claim 54 wherein the flow is controlled by electro-osmosis, electrophoresis, dielectrophoresis, pressure gradient, microvalve, optical trapping and flow stoppage.

44. A method of claim 43 wherein the flow control is provided by a voltage gradient between the branch channels and the junction.

45. A method of claim 44 wherein the voltage gradient is generated by electrodes in the branch channels.

46. A method of claim 44 wherein the main channel comprises an electrode.

47. A method of claim 43 wherein the flow control is by a pressure gradient between one or more channels and the junction.

48. A method of claim 43 wherein the pressure gradient is provided by capillary action at one or more channels of the substrate.

49. (Amended) A method of claim 54 wherein the flow control comprises one or more valves.

50. (Amended) A method of claim 54 wherein the flow is reversible.

51. (New) A device for processing a flow of biological material, said device comprising a substrate having an analysis unit microfabricated thereon and comprising:

(a) a main channel having a sample inlet, a detection region downstream of the sample inlet, and a branch point discrimination region adjacent to and downstream of the detection region;

(b) at least two branch channels originating at the branch point discrimination region and in communication with the main channel; and

(c) a flow control system adapted to direct each particle into a selected branch channel.

52. (New) A device according to claim 51 wherein the flow control system is responsive to a detection apparatus for evaluating the biological material according to at least one characteristic as the material passes through the detection region.

53. (New) A device according to claim 4 wherein the silicon elastomer comprises PolyDiMethylSiloxan (PDMS).

54. (New) A method for sorting cells according to a predetermined characteristic, which method comprises:

(a) flowing a sample of cells through the main channel of a device according to claim 51 so that on average one cell at a time is placed within the detection region;

(b) interrogating each cell for the predetermined characteristic as it passes through the detection region; and

(c) directing the flow of each cell into a selected branch channel according to the results of the interogation.

REMARKS

The present application is a divisional of copending U.S. Patent Application Serial No. 09/325,667 filed on May 21, 1999 (hereinafter the "parent

application"). The parent application was originally filed with claims 1-50, and these original claims are included in the specification submitted herewith. Claims 1 and 38 have been canceled in this Preliminary Amendment, without prejudice to Applicants' right to pursue the subject matter of those canceled claims in either the instant or in other (*e.g.*, related) patent applications. Claims 2-14, 16, 18-28, 31-35, 39-43, 49 and 50 have been amended and new claims 51-54 have been added. Therefore, with entry of this Preliminary Amendment claims 2-37 and 39-54 will be pending in the instant divisional application.

More specifically, claims 1 and 38 have been canceled without prejudice and in favor of new claims 51-52 and 54. These new claims have been added in order to broadly claim preferred embodiments of the Applicants' invention that were not specifically claimed in the parent application. Claims 2-14, 16, 18-28, 31-35, 39-43, 49 and 50 have been amended to depend from and/or incorporate terms of the new claims. Finally, claim 53 has been added to recite particularly preferred embodiments of the invention; namely, embodiments wherein the claimed devices are manufactured from PolyDiMethylSiloxan (PDMS) (see, for example, at line 11 on page 60 of the specification as originally filed). The specification has also been amended

The specification of this application has also been amended. In particular, a new sentence has been added at the beginning of the specification to

include a specific reference to the prior provisional application and pursuant to 37 C.F.R. § 1.78.

The amendments to the specification and claims have been made pursuant to the requirements of Rule 121 of the Rules of Practice. Specifically, the amended paragraphs in the specification and the pending claims are written above, in clean form as amended, pursuant to the requirements of 37 C.F.R. § 1.121(b)(1)(ii) and §§ 1.121(c)(1)(i) and (c)(3). Pursuant to the requirements of 37 C.F.R. § 1.121(b)(1)(iii) and (c)(1)(ii), another version of the amended paragraphs and claims is attached hereto as Exhibit A. This other version has been marked up to show all changes made in this amendment relative to the each paragraph and claim as originally filed in the parent application. The amendments do not constitute new matter. Accordingly, entry of these amendments into the file history of the present divisional application is respectfully requested.

Respectfully submitted,

Dated: August 13, 2001

Samuel S. Woodley

Samuel S. Woodley, Ph.D.
Reg. No. 43,287
Agent for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

EXHIBIT A

EXHIBIT A:
AMENDMENTS MADE IN
DIVISIONAL U.S. PATENT APPLICATION SERIAL NO. To Be Assigned
(FILED CONCURRENTLY HEREWITH)

ATTORNEY DOCKET NO. 3153/1E974-US2

IN THE SPECIFICATION:

The paragraph at lines 4-8 on page 1 of the specification should be amended as follows:

This application is a divisional of copending U.S. Patent Application Serial No. 09/325,667 filed on May 21, 1999 (hereinafter "the '667 application"). The '667 application, in turn, claims the benefit of priority from U.S. Patent Application No. 08/932,774, filed September [25] 23, 1997 (now U.S. Patent No. 6,221,654 B1, issued April 24, 2001), and is a continuation-in-part thereof[;]. The '667 application also claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/108,894 filed November 17, 1998; and to U.S. Provisional Application No. 60/086,394 filed May 22, 1998 [each]. Each of these priority applications is incorporated herein by reference in [their entireties] its entirety.

IN THE CLAIMS:

Claims 2-14, 16, 18-28, 31-35, 39-43, 49 and 50 should be amended as follows:

2. (Amended) A device of claim [1] 51, wherein at least one of the main and [outlet] branch channels communicates with a reservoir.

3. (Amended) A device of claim [1] 51, wherein the substrate is comprised of silicon.

4. (Amended) A device of claim [1] 51, wherein the substrate comprises a silicone elastomer.

5. (Amended) A device of claim [1] 51 wherein the particles of biological material [comprises] comprise cells.

6. (Amended) A device of claim 4 wherein the silicone elastomer substrate is made from an impression of an etched silicon wafer.

7. (Amended) A device of claim [1] 51 wherein the flow control system is electro-osmotic.

8. (Amended) A device of claim [1] 51 wherein the flow control system is electrophoretic.

9. (Amended) A device of claim [1] 51 wherein the flow control system is dielectrophoretic.

10. (Amended) A device of claim [1] 51 wherein the flow control system is pressure driven.

11. (Amended) A device of claim [1] 51 wherein the flow control system is microvalve.

12. (Amended) A device of claim [1] 51 wherein the flow control system is optical trapping.

13. (Amended) A device of claim [1] 51 wherein the flow control system is flow stoppage-based control.

14. (Amended) A device according to claim [1] 51 wherein the flow control is provided by a voltage gradient between the branch channels and the junction.

16. (Amended) A device of claim [1] 51 wherein the flow control is by a pressure gradient between one or more channels and the junction.

18. (Amended) A device of claim [1] 51 wherein the flow control comprises one or more valves.

19. (Amended) A device of claim [17] 51 wherein the flow control comprises one or more valves.

20. (Amended) A device of claim [1] 51 wherein the flow control is reversible.

21. (Amended) A device of claim [1] 52 wherein the characteristic is optically detectable.

22. (Amended) A device of claim [1] 52 wherein the characteristic is determined by a fluorescent reporter.

23. (Amended) A device of claim [1] 52 wherein the characteristic is determined by a chemiluminescent reporter.

24. (Amended) A device of claim [1] 52 wherein the characteristic is determined by a radioactive reporter.

25. (Amended) A device of claim [1] 52 wherein the characteristic is determined by a spectroscopically detectable reporter.

26. (Amended) A [micro-fabricated sorter] device according to claim [1] 52 wherein the predetermined characteristic is size.

27. (Amended) A device of claim [1] 52 wherein the detection apparatus comprises a light scattering apparatus.

28. (Amended) A device of claim [1] 52 wherein the detection apparatus comprises an apparatus for recognizing electromagnetic radiation.

31. (Amended) A device of claim [1] 52 wherein the detection apparatus comprises at least one of photomultiplier tubes and photodiodes.

32. (Amended) A device of claim [1] 52 wherein the detection apparatus is positioned to target biological materials within a predetermined detection region.

33. (Amended) A device of claim [1] 51, wherein the width and height of a channel of the device is at least about two times as large as the diameter of the largest material to be sorted.

34. (Amended) A device of claim [1] 51, wherein a channel is from about 20 μm to 200 μm wide and about 20 μm to 200 μm deep.

35. (Amended) A device of claim [1] 51, wherein the biological material is a cell having a predetermined characteristic that is identified according to a reporter signal selected from a dye, fluorescent agent, chemiluminescent agent, chromophore, radio-isotope, and optically detectable protein.

39. (Amended) A method of claim [38] 54 wherein the width and height of each channel is at least about two times as large as the diameter of the largest cell in the [mixture] sample of cells.

40. (Amended) A method of claim [38] 54 wherein the predetermined characteristic is an optically detectable reporter in or on the cells.

41. (Amended) A method of claim [38] 54 wherein the cells are interrogated by at least one device selected from the group of microscopes, diodes, light stimulating devices, lasers, light scattering apparatuses, electromagnetic excitation sources, electromagnetic radiation detector apparatuses, photomultiplier tubes, and processors.

42. (Amended) A method of claim [38] 54 wherein the reporter is selected from a dye, fluorescent agent, chemiluminescent agent, chromophore, radio-isotope, and optically detectable protein.

43. (Amended) A method of claim [38] 54 wherein the flow is controlled by electro-osmosis, electrophoresis, dielectrophoresis, pressure gradient, microvalve, optical trapping and flow stoppage.

49. (Amended) A method of claim [38] 54 wherein the flow control comprises one or more valves.

50. (Amended) A [device] method of claim [38] 54 wherein the flow is reversible.